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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/729,658	12/04/2000	Jonathan Zonana	6005-55924	3101

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EXAMINER

MARVICH, MARIA

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/729,658

Applicant(s)

ZONANA ET AL.

Examiner

Maria B Marvich, PhD

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4, 22-26, 41, 42 and 59-64 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4, 22-26, 41, 42 and 59-64 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 04 December 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>4/23/01</u> . | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

This office action is in response to a Response to a Restriction Requirement filed 4/9/04. Claims 5-21, 27-40 and 43-58 have been cancelled. Claims 59-64 have been added. Claims 1-4, 22-26, 41-42 and 59-64 are pending in the application.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-4, 22-26 and 41-42) in the amendment filed 4/23/04 is acknowledged. Added Claims 59-64 are directed to elected subject matter and, therefore, claims 1-4, 6-22, 41-42 and 59-64 are under examination in this application.

Information Disclosure Statement

An IDS filed 4/23/01 has been identified and the documents considered. The signed and initialed PTO Form 1449 has been mailed with this action.

Claim Objections

Claims 2-4 and 42 are objected to because of the following informalities: in claims 2-4, the article "the" is missing prior to the phrase "method is a method of". Claim 42 recites the abbreviations "XLHED" and "HED" without defining them. Appropriate correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

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pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 59-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants recite a genus of protein fragments and amino acid substitution mutants of SEQ ID NO: 2 and a genus of fusion proteins comprised of SEQ ID NO: 2 for use in a method of increasing EDA1-II activity.

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

In the instant case, applicants only disclose SEQ ID NO: 2, which correspond to the amino acid sequence of EDA1-II, a splice variant of EDA1. EDA1-II isolated from ectodermal diseases such as XLHED and HED or alopecia contains multiple mutations in exons 3-9. Accordingly, applicants have proposed that an increase of EDA1-II activity by administration of the recited EDA1-II proteins would lead to the development of hair follicles, teeth and sweat glands. Claims 59-64 are directed to fragments of EDA1-II that comprise between 153 and 300 amino acids of SEQ ID NO: 2, fusion proteins with SEQ ID NO: 2 and mutants of SEQ ID NO:

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2 with 1-10 amino acid substitutions. The specification teaches methods that can be utilized to produce protein sequence variants (page 30, paragraphs 319-323 and page 31, paragraph 0337 through page 32, 341). Specifically, it is indicated that fragments 133-391, 153-391 and 239-391 possess the same activity as SEQ ID NO: 2. However, no other fragments or fusions or mutants of SEQ ID NO: 2 are envisioned to increase hair follicle development, tooth development or sweat gland development. Neither applicant nor the prior art provide a correlation between the structure of the recited sequences and ability to induce development of hair follicles, teeth or sweat glands. Given the diversity and large size of the genus of fragments, fusions and mutations of SEQ ID NO: 2, and the inability to determine which will also have the recited ability, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of the broadly claimed genus.

Claims 1-4, 22-26, 41-42 and 59-64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat.

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App. & Inter, 1986) and *In re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention.** The invention recites a method of increasing hair follicle, tooth or sweat gland development by increasing EDA1-II activity.

2) **Scope of the invention.** The method recites administration of EDA1-II protein to the tissues to increase EDA1-II activity in humans suffering from ectodermal disease. This invention uses methods of protein therapeutics.

3) **Number of working examples and guidance.** Applicants teach several prophetic assays that are designed to identify agents that enhance EDA1-II activity on page 4, paragraph 0069. These include proposed *in vivo* methods that involve intradermal injection or topical application of the protein to the skin or tails of newborn tabby mice and detection of the induction of hair growth and injection of proteins into footpads of newborn tabby mice and monitoring of sweat gland development. Proposed *in vitro* assays include application of protein to dissected skin from mouse embryos and calculation of hair follicles that follow as well as application of truncated protein to an *in vitro* tooth organ culture system.

Once proteins that enhance EDA1-II activity have been identified, it is taught that the protein can be used in therapeutic applications. Specifically, it is disclosed that purified protein at concentrations ranging from 1 ng/ml to 1 g/ml is applied to the tails, bellies and areas behind the ears of newborn tabby mice, wild type mice and nude mice (see page 28, paragraph 0307) or is injected into footpads of newborn tabby mice (See page 28, paragraph 0309). Alternatively, the protein can be applied to *in vitro* tooth cultures and the teeth introduced into humans or other organism (see page 28, paragraph 0308).

There is no actual introduction of the recited proteins *in vivo* in animal models or in humans. Nor are there proposed methods for the application of the recited methods for human use.

4) **State of Art.** The state of art for treatment of humans suffering from ectodermal dysplasia is not currently a high art. Cosmetic or functional correction is the only recourse patients have against this disease (see e.g. MedlinePlus medical encyclopedia). However, methods based on protein therapeutics for treatment of ectodermal dysplasia is a high art.

Torchilin and Lukyanov teach that there are many unresolved problems concerning the delivery of proteins and peptides such as rapid elimination from the circulation through renal filtration, enzymatic degradation, uptake by the reticuloendothelial system and accumulation in non-targeted organs and tissues and inefficient cell entry (see Box 1, page 260).

Recently, permanent correction of ectodermal dysplasia in tabby mice has been reported (see Gaide and Schneider). In this study, application of EDA1 was conducted in pregnant tabby mice by serial intravenous injections of 400 µg of recombinant EDA1 (in 2mg/ml PBS) following two different dose schedules. Newborn mice received a single intradermal injection at the same dose (see Gaide and Schneider, bridging paragraph page 617-618). Formation of hair, teeth and sweat glands were induced in the newborn mice.

5) **Unpredictability of the art.** It is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the claimed therapeutic strategy and applicants present no disclosed or art recognized nexus between the xenograft and nude mice experimental models and the human disease state. “Although animal studies have suggested low toxicity and excellent efficacy, these investigation have been limited by the use of immuno-

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deficient mice” (Meng and Deiry, p. 6, column 1). The success of any *in vitro* assays or *in vivo* animal models cannot be considered as evidence of success of treatment, *in vitro* results rarely correlate well with *in vivo* clinical trial results in patients and have not translated into successful human therapies.

Furthermore, any successes in the published document by Gaide and Schneider cannot be extrapolated back to the instant invention because the instant specification lacks support for the teachings of the reference. The teachings of the instant invention differ from that of Gaide and Schneider. Neither the specification nor the teachings of Gaide and Schneider provide adequate guidance for the application of EDA1-II to humans for the treatment of ectodermal dysplasia. Problems with protein therapeutics identified in the art are not addressed by the methods of the instant invention nor the prior art. Therefore, neither the specification nor art teach one how to treat ectodermal dysplasia by introduction of EDA1-II as neither the specification nor the prior art provide dosages of EDA1-II to administer to patients, schedule of treatments, specific modes of administration of EDA1-II to humans suffering from ectodermal disease is provided.

6) **Summary.** The invention recites a method of treating ectodermal disease by the administration of EDA1-II protein to a subject using gene therapy. The unpredictability of using the claimed invention in gene therapy is accentuated due to the lack of methods or processes disclosed in the instant specification that exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a

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claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

May 10, 2004


GERRY LEFFERS
PRIMARY EXAMINER